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Vasopressin-prostaglandin interactions in the regulation of epithelial cell permeability to water

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Prostaglandins (PG's) have effects at several sites involved in the regulation of water balance. Many of these are discussed elsewhere in this symposium. This review will consider vasopressin-PG interactions that are involved in the regulation of water permeability of epithelia, particularly the renal collecting duct and toad urinary bladder. It is well established that the increase in permeability to water that vasopressin elicits in epithelia involves stimulation of the formation of cyclic AMP [1] and that PGE inhibits the water permeability response by inhibiting the stimulation of cyclic AMP formation [2, 3]. After summarizing the current understanding of the cellular action of vasopressin and the development of ideas and information regarding the role of PG's in regulating the response to vasopressin, the mechanisms of the effects of PG's will be considered, as well as the effect of vasopressin on the metabolism of PG's and related compounds. Finally, the foregoing will be considered in terms of normal and abnormal regulation of water permeability.

Effect of vasopression on permeability and transport

Vasopressin affects water permeability by binding to specific receptors in the basal-lateral plasma membrane of the epithelial cells. The binding is normally coupled to and activates the catalytic unit of adenylate cyclase in the plasma membrane, resulting in increased formation and accumulation of cyclic AMP within the epithelial cell. The elevated level of cyclic AMP induces changes in the apical plasma membrane that are manifested as increased permeability to water and to small slightly lipophilic solutes and increased transport of sodium from urine to blood. In toad urinary bladder and skin and perhaps in medullary collecting duct, there is also increased permeability to urea and related amides. Based on studies with toad urinary bladder, it appears that each of the permeability changes and the stimulation of sodium transport may be mediated by a separate vasopressin-sensitive adenylate cyclase and related pool of cyclic AMP [4]. The changes in the apical plasma membrane have been characterized on the basis of indirect evidence. Each of the changes in permeability and the increase in sodium transport appears to be a manifestation of a separate and perhaps independent alteration in the apical membrane. There is no direct evidence as to how cyclic AMP elicits these effects. That aspect of the physiology of the response to vasopressin, reviewed in more detail elsewhere [5–7], is not of immediate concern to this discussion because PG's affect cyclic AMP formation. There is no evidence that PGE or other arachidonic acid derivatives act at a more distal step as well.

Inhibition by PGE

It is clear that PGE inhibits the vasopressin-stimulated adenylate cyclase that mediates the water permeability response. The initial evidence was the inhibition by PGE of the water permeability response to vasopressin without inhibition of the water permeability response to exogenous cyclic AMP in toad urinary bladder [2] and isolated perfused cortical collecting duct of the rabbit [3]. The observations in toad urinary bladder have been confirmed [8–10], and additional support is provided by the demonstration that the accumulation of cyclic AMP in the epithelial cells of the bladder [11] and in slices of renal medulla [12] exposed to vasopressin is reduced by low concentrations of

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PGE. The urea permeability response to vasopressin is inhibited by PGE in toad urinary bladder, but sensitivity to inhibition is less than that of the water permeability response [10]. Modest inhibition by PGE of the short-circuit current response to vasopressin in toad urinary bladder has been reported by one laboratory [13] but not confirmed by another [8, 14]. In isolated perfused rabbit cortical collecting duct, PGE inhibits sodium transport [15, 16]. When this segment is exposed to physiologic levels of vasopressin, sodium transport increases transiently and then falls to rates below control. The reduction in sodium transport to below the control rate is prevented by meclofenamate. In the presence of meclofenamate, it is elicited by PGE [17].

Effect of PGE on adenylate cyclase

Two factors complicated the interpretation of the early experiments. The first is that in toad urinary bladder there is "receptor reserve" for cyclic AMP accumulation relative to the water permeability response [18]. High concentrations of vasopressin elicit cyclic AMP production that exceeds the level required to elicit the maximal water permeability response. When adenylate cyclase activity is inhibited by PGE, cyclic AMP production in response to high concentrations of vasopressin is reduced but is still sufficient to elicit the full water permeability response, yielding kinetics that superficially appear to be the result of competitive inhibition by PGE. The second complication is that in toad urinary bladder, as in many other tissues, high concentrations of PGE stimulate adenylate cyclase. In the initial report of the inhibitory effect of PGE in toad bladder, it was noted that in one series of experiments with a high concentration of PGE (1 μM) the water permeability response to theophylline (an inhibitor of the degradation of cyclic AMP) was enhanced [2]. Subsequently, the enhancement of water flow by high concentrations of PGE in the presence of theophylline was clearly demonstrated [14] and related to elevated levels of cell cyclic AMP [11, 14]. In the isolated perfused cortical collecting duct, high concentrations (100 μM) of PGE alone increase water permeability, as do low concentrations (1 μM) in the presence of theophylline [3]. In addition, in toad urinary bladder [8], but not in collecting duct [15, 16], in high concentrations, PGE alone has a small stimulatory effect on sodium transport, undoubtedly the result of increased cyclic AMP production.

The molecular basis of the inhibitory effect of PGE on vasopressin-stimulated adenylate cyclase is not known. All of the foregoing concepts regarding the action of PG's are based on studies with intact cells. Although small changes have been noted [12, 19, 20], the inhibitory effect of PGE on hormone-stimulated adenylate cyclase activity has not been demonstrated convincingly in assays of the enzyme in broken cell preparations, or in "permeabilized" medullary collecting ducts dissected from rat kidney [21]. This failure applies as well to PGE inhibition of hormone-stimulated adenylate cyclase in other tissues such as fat cells. Apparently, an essential factor is missing, or some factor in the standard adenylate cyclase assay interferes with the demonstration of the inhibitory effect. The situation may be viewed in terms of a model proposed recently [22]. In this model, there are three components of adenylate cyclase involved in hormonal stimulation of cyclic AMP production. The components are: *(1)* receptors for the hormone, *(2)* the catalytic subunit, and *(3)* a guanine-nucleotide-binding subunit that couples hormone receptors to the catalytic subunit—in cells subject to inhibition of adenylate cyclase by specific factors such as PG's, there are two additional components in the plasma membrane, *(4)* receptors for the inhibitor (PG's, and in fat cells adenosine and nicotinic acid as well [23]), and *(5)* a guanine-nucleotide-binding subunit that couples the receptors for inhibitor with adenylate cyclase. One would anticipate that all five components are present in toad urinary bladder and in collecting duct. In addition, there are probably receptors for PG's (or a related material) that are coupled to adenylate cyclase in a mode that stimulates the enzyme. This would explain the stimulatory effect of high concentrations of PGE on cyclic AMP accumulation and on water permeability and sodium transport.

Production of prostaglandins by vasopressin-sensitive tissues

Twelve years ago, Grantham and Orloff [3] suggested that PG's, formed within vasopressin-sensitive cells, would serve to dampen the effects of vasopressin, thereby modulating the water permeability response. Subsequent work in a number of laboratories has established that PGE is made by vasopressin-sensitive tissues and ordinarily exerts an inhibitory effect on the response to vasopressin. Initially, it was shown that in the toad urinary bladder, inhibitors of the synthesis of PG's [13, 24, 25] and an antagonist of the action of PG's [13, 26] enhanced the water permeability response to vasopressin. A similar pattern has been found in the

mammalian kidney. Inhibitors of PGE synthesis enhance the renal medullary accumulation of cyclic AMP [12, 27] and the antidiuretic response of kidney to vasopressin [27–29]. There is evidence that the epithelial cells synthesize PGE. Arachidonic acid cyclooxygenase, an enzyme involved in PGE biosynthesis, has been demonstrated in collecting duct cells by immunofluorescence [30] and epithelial cells scraped from toad urinary bladder produce PGE (Halushka P, personal communication).

An important issue under current study is whether vasopressin affects PGE biosynthesis or the biosynthesis of other arachidonic acid derivatives, which in turn might affect the response to vasopressin. Because PGE and other arachidonic acid derivatives do not accumulate in cells but are released into extracellular fluids, the rate of PGE biosynthesis in vitro is usually estimated by measuring the rate of appearance of PGE in Ringer's solution. Two laboratories have observed that vasopressin stimulates the release of PGE by the toad urinary bladder [31, 32]. The release of PGE is elicited by the same low concentrations of vasopressin that elicit the water permeability response [31], and it occurs as rapidly [31, 33]. In the foregoing experiments, PGE was quantified by radioimmunoassay. About 95% of the PGE appeared in the serosal solution, 5% in the mucosal solution [31]. To determine the step at which vasopressin stimulates PGE biosynthesis, bladders were incubated with ^{3}H-arachidonic acid to label cell stores of the precursor of PGE. After a control period and after the bladder was incubated with vasopressin, fatty acids released into the serosal solution were collected and separated by thin-layer chromatography, and their radioactivity was quantified. Radioactivity was increased in regions corresponding to arachidonic acid and to PGE, indicating that the hormone acted by stimulating the release of arachidonic acid. This has been found to be the rate-limiting step in PGE biosynthesis in renal medullary interstitial cells [34] and other tissues [35].

The stimulation of PGE biosynthesis in the toad bladder by vasopressin has not been confirmed in studies from two other laboratories [36] (Bisordi, Schlondorff, and Hays, personal communication). Although there is a difference in analytical technique, this does not appear to explain the difference in results. Increased production was observed in laboratories using the same assay, one that relies on an antibody to PGB. PGB and other prostanoids are removed by chromatography, and then PGE is converted to PGB and assayed by radioimmunoassay. Negative results were obtained in laboratories using an antibody to PGE. Both methods are apparently quite specific for PGE in terms of recovery of PGE added to a sample and the lack of interference by other known compounds. I can only speculate on the cause of the different results. It is possible that an unknown prostanoid is synthesized in response to vasopressin and crossreacts with the antibody to PGB but not with the antibody to PGE. Seasonal differences in the effect of vasopressin on PGE production have been noted [32] and might have contributed to the differences between the two groups. Unrecognized manipulation of the toad or the bladder may have obscured or emphasized the effect of vasopressin. At this time, there is no reason to favor any of the foregoing as the explanation for the different results.

The evidence regarding vasopressin stimulation of PGE biosynthesis in mammalian kidney is also conflicting in that there are species differences. In addition, the evidence is difficult to evaluate, for only urinary PG's have been assayed. Urinary PG's include a portion of circulating PG's that were filtered or secreted into tubule fluid as well as PG's that were synthesized within the kidney [37]. The secretory system for PG's in proximal straight tubule is inhibited by probenecid and by nonsteroidal antiinflammatory organic acids (indomethacin, naproxen, ibuprofen) that also inhibit PGE biosynthesis [38–40]. Renal medullary interstitial cells synthesize PGE. There is no question that the rate of PGE biosynthesis by these cells in culture is stimulated by vasopressin, as well as by bradykinin and by angiotensin II [41]. All of these agents act by stimulating the release of arachidonic acid, the precursor of PGE, from storage sites such as phospholipids [34]. Stimulation of these cells by vasopressin appears to involve receptors that recognize analogs of the hormone with pressor rather than antidiuretic activity (Beck, Hassid, and Dunn, personal communication). 1-Desamino-8-D-arginine vasopressin (dDAVP), a synthetic analog with antidiuretic activity but no pressor activity, has no effect on PGE biosynthesis by the cells in culture. Biosynthesis is stimulated by analogs with pressor activity, and this stimulation can be blocked by d$(CH_2)_5$VD-AVP [1-β-mercapto-β,β-cyclopentamethylene propionic acid, 4-valine,8-D-arginine] vasopressin, a synthetic nonpressor, nonantidiuretic antagonist of vasopressin's pressor activity. Although these cells are located in the interstitium of the medulla, it is not clear that PG's released at this

site would enter the urine or reach vasopressin-sensitive epithelial cells in the cortex of the kidney. There is evidence that collecting duct cells can synthesize PG's [21, 30]. If PGE synthesized by the collecting duct distributes as it does in toad urinary bladder [31], less than 10% of the PGE synthesized in these vasopressin-sensitive cells would appear in the urine. Quantitative evaluation of renal metabolism of PGE has been discussed in detail in a recent review [37]. One must conclude that measurement of urinary PG's will yield information of limited value until more is known about the source of urinary PGE.

Urinary excretion of PG's has been found to be increased by vasopressin in some but not all species. In rats with hereditary pituitary diabetes insipidus, urinary excretion of PGE is low and is increased, as it is in normal rats, by injection of vasopressin [42, 43] or by oral administration of dDAVP [43]. Vasopressin increases urinary PGE excretion in rabbits [44], but not in dog [45] or in man [46]. In dog [45] and in man [46], PGE excretion rate appears to vary directly with urine flow rate.

I am aware of only one study that indicates an effect of vasopressin on PG biosynthesis by the collecting duct. The evidence is indirect and was obtained in experiments with the isolated rabbit cortical collecting duct perfused in vitro with an isotonic salt solution. PGE alone has been shown to inhibit lumen-to-bath sodium transport in this segment [15, 16]. Vasopressin elicits an increase in the rate of sodium transport [47]. The increase is usually transient; sodium transport falls to control levels in 30 min [17, 47]. The fall in sodium transport rate is blocked by meclofenamate, an inhibitor of cyclooxygenase activity and thus of PG biosynthesis. After treatment with meclofenamate and vasopressin, if PGE is added, the rate of sodium transport falls [17]. The simplest explanation of these observations is that vasopressin stimulates adenylate cyclase activity and thereby stimulates sodium transport. Vasopressin also stimulates the production of PGE or a similar prostanoid whose biosynthesis depends on cyclooxygenase activity. PGE or the related prostanoid inhibits vasopressin-stimulated adenylate cyclase and sodium transport in this segment. Transepithelial electrical potential difference and lumen-to-bath transport of chloride, calcium, and phosphate ions respond as sodium transport responds to vasopressin, meclofenamate, and PGE [48]. It will be important to confirm these interesting results that expand the list of transport processes known to be affected by vasopressin and by PGE. It may be possible to study the effect of vasopressin on the biosynthesis of PGE in isolated collecting ducts using principles similar to those used to study vasopressin-sensitive adenylate cyclase in dissected nephron segments [49]. In a recent study it was shown that isolated medullary collecting ducts dissected from rat kidney convert ^{3}H-arachidonic acid to material that behaves like PGE_2 and $PGF_{2\alpha}$ chromatographically [21]. It should be possible to label cell stores of arachidonic acid by incubating dissected nephron segments with ^{3}H-arachidonic acid. Metabolites released in response to vasopressin or to a nonpressor analog with antidiuretic activity such as dDAVP, can be separated chromatographically and the derivatives identified to a reasonable degree based on the chromatographic behavior of standards. Physical manipulation is known to stimulate PG biosynthesis in tissues. The dissection and other manipulations of the tubule in vitro may have such an effect, which could obscure changes in PG biosynthesis elicited by vasopressin later in the experiment. For example, in the studies in which meclofenamate affected the electrolyte transport response to vasopressin, collection periods were begun 300 min after dissection and canulation of the tubule [17, 48].

Manipulation of the rate of prostaglandin biosynthesis

Regardless of whether vasopressin stimulates PGE biosynthesis, it is evident that in the presence of vasopressin, toad urinary bladder and mammalian kidney synthesize PG's at rates sufficient to inhibit the adenylate cyclase response to the hormone [13, 24, 25, 27]. Therefore, changes in the rate of PG biosynthesis will be associated with an opposite change in the response to vasopressin. Agents such as the nonsteroidal antiinflammatory agents that inhibit PG synthetase enhance the water permeability response to vasopressin. Sulfonylureas, such as chlorpropamide acting like the nonsteroidal antiinflammatory agents, have a similar effect in toad urinary bladder [50]. Sulfonylureas increase urinary osmolality in some patients with pituitary diabetes insipidus [51] and in diabetes insipidus rats given dDAVP [52]. It has not been established whether these agents act on the kidney as they do in toad urinary bladder by inhibiting PG biosynthesis.

Adrenal steroid hormones enhance the water permeability, sodium transport, and urea permeability response of the toad urinary bladder to vasopressin [53]. The enhancement is in part the result of reduced cyclic nucleotide phosphodiester-

ase activity in bladder epithelial cells incubated with adrenal steroids [54], and in part the result of reduced PG biosynthesis [55]. Toad urinary bladder can be depleted of the effect of adrenal steroid hormones by several hours of incubation in vitro without steroids. In the absence or presence of vasopressin, depleted bladders synthesize more PG than do bladders incubated with adrenal steroid hormones. Examination of metabolites released from bladders labeled with ^{3}H-arachidonic acid revealed that incubation with adrenal steroid hormones results in inhibition of acylhydrolase activity that catalyzes the release of arachidonic acid from tissue stores [55]. Adrenal steroid hormones have this effect in other tissues that synthesize PG's. This is regarded as a glucocorticoid effect [56]. It is probably a glucocorticoid effect in toad urinary bladder but glucocorticoid-mineralocorticoid differences are not well defined in amphibia [57]. Adrenal steroid hormones have a similar effect in mammalian renal medullary interstitial cells in culture [56] and perhaps in the collecting duct as well. There is a renal concentrating defect in animals with adrenal insufficiency [58–60]. In a recent study [60], the water permeability response to 200 μU/ml of arginine vasopressin was markedly depressed in isolated perfused cortical collecting ducts taken from adrenalectomized rabbits. The depressed responsiveness returned to normal 2 hours after the addition of 50 pM aldosterone or 50 pM dexamethasone in vitro. In additional experiments, the water permeability response to 0.1 mM 8-Br-cyclic AMP was normal in collecting ducts from adrenalectomized rabbits as was the response to a lower concentration (2 μU/ml) of vasopressin in the presence of 0.1 mM 1-methyl-3-isobutylxanthine, a cyclic AMP phosphodiesterase inhibitor. Because all of the normal responses, including those of the tubules from adrenalectomized rabbits, were maximal permeability responses, some of the additional experiments may not have been sensitive enough to detect reduced responsiveness. Cyclooxygenase inhibitors have not been used to examine the role of endogenous PG's in the water permeability response of the isolated cortical collecting duct of normal rabbits to vasopressin. Whether PG's play a role in the depressed water permeability response of the cortical collecting duct of adrenalectomized rabbits also remains to be determined. Because there is a renal concentrating defect [57–59], it might be fruitful to study renal PG metabolism and the response to vasopressin in adrenalectomized animals. It is interesting to note the very low concentration (5 pM) of aldosterone or dexamethasone that reversed the defect in vitro, indicating marked sensitivity to a mineralocorticoid or glucocorticoid hormone.

Prostaglandin production may also be affected by pH. The water permeability response of the toad urinary bladder to vasopressin is inhibited as serosal pH is lowered, whereas the response to cyclic AMP is unaffected or enhanced [61, 62]. Apparently PGE production increases as pH of the serosal solution is lowered from a pH of 8.0 to 7.4, a pattern compatible with the suggestion that serosal acidification inhibits the water flow response to vasopressin in part by stimulating the biosynthesis of PGE [36].

Effect of other arachidonic acid derivatives

In view of the large and increasing number of arachidonic acid derivatives that have been identified and found to be active in a variety of tissues, it is possible that derivatives other than the PG's affect the response to vasopressin. Recent work has provided evidence that thromboxane A_2 may affect water permeability of the toad urinary bladder. Initially, thromboxane B_2, the metabolite of thromboxane A_2, was identified by gas chromatography mass spectroscopy in Ringer's solution in which bladders had been incubated [32]. In that study, thromboxane B_2 and PGE were quantified by radioimmunoassay. Both derivatives were found in the Ringer's solution bathing the serosal surface of the bladder. The biosynthesis of both was increased by vasopressin during the period of the water permeability response. In additional studies, indirect evidence was obtained that thromboxanes, synthesized in response to vasopressin, have a stimulatory effect on the water permeability response. An inhibitor of thromboxane biosynthesis, 7-(1-imidazolyl)-heptanoic acid (7-IHA) inhibited thromboxane B_2 production and the water permeability response to vasopressin without affecting PGE production. Similarly, a thromboxane antagonist, 13-azaprostanoic acid (13-APA), inhibited the water permeability response to vasopressin. The inhibitory effects of 7-IHA and of 13-APA were dependent on endogenous thromboxane biosynthesis in that they had no effect if thromboxane and PGE biosynthesis were inhibited by meclofenamate or indomethacin [33]. Neither 7-IHA or 13-APA affected the water permeability response to cyclic AMP, perhaps because cyclic AMP does not stimulate thromboxane biosynthesis [33], or because thromboxanes, like PGE, act at a step that affects the production of cyclic AMP. When the effects of endogenous

thromboxanes were inhibited, the maximal inhibition of water flow was about 30%, indicating that the portion of the water permeability response to vasopressin that is enhanced by vasopressin-stimulated thromboxane biosynthesis is not large.

In view of the indirect nature of the foregoing evidence, attempts have been made to stimulate water flow directly with thromboxanes or thromboxane-like agents [63]. In these experiments, the effects of endogenous arachidonic acid derivatives were eliminated by incubating bladders in meclofenamate or indomethacin. Because the active derivative thromboxane A_2 is relatively unstable, thromboxane B_2 in high concentrations (25 μM) and two stable PG endoperoxide analogs that have been shown to have thromboxane-A_2-like effects in other tissues were tested. Each of the agents alone increased the water permeability of the bladder. The effect of the thromboxane-like agents was blocked by 13-APA, the thromboxane antagonist that inhibited the water permeability response to vasopressin. The foregoing evidence supports the suggestion that vasopressin stimulates thromboxane A_2 biosynthesis by the toad urinary bladder and that thromboxane A_2 elicits part of the increase in permeability to water [63]. In a preliminary report [64], however, the endoperoxide analogs inhibited the water permeability response of the toad urinary bladder to vasopressin. The discrepancy between the reports has been attributed to another effect of the endoperoxide analogs. They cause contraction of the smooth muscle of the bladder. In view of this additional effect, which could easily distort estimates of water permeability, it would be better to test these agents on the water permeability of frog or toad skin or the isolated perfused cortical collecting duct. If the stimulatory effect of thromboxanes on water permeability is confirmed, it will be important to ascertain whether thromboxane A_2 acts by stimulating adenylate cyclase, as would seem likely. Although thromboxanes and PGE usually have opposing effects, it may be that the stimulation of water permeability by high concentrations of PGE is the result of interaction with receptors for thromboxane A_2.

Homogenates of renal cortex and of renal medulla can synthesize prostacyclin (PGI_2), thromboxane A_2, and $PGF_{2\alpha}$, as well as PGE_2 [65]. The role of the other derivatives in the renal response to vasopressin is unknown. The effect of some of the other arachidonic acid derivatives has been examined in toad urinary bladder. PGF, PGA, and PGB were less potent than was PGE as inhibitors of the water permeability response to vasopressin [9].

Biological importance of the inhibition of adenylate cyclase by prostaglandin E

There is now abundant evidence to support the suggestion [3] that PGE synthesized in vasopressin-sensitive cells dampens the water permeability response to vasopressin. PGE and other arachidonic acid derivatives may have a more complex role as well. It is apparent that changes in the response to vasopressin can be produced by changes in the rate of PGE biosynthesis. Therefore, regulation of the pathway for PG biosynthesis may serve as a pathway by which the response to vasopressin is regulated by other factors, for example, the marked effect of adrenal steroid hormones [53, 60]. Furthermore, in view of the evidence that the water permeability, urea permeability, and sodium transport responses to vasopressin have different sensitivity to the inhibitory effect of PGE [10, 13], changes in PGE biosynthesis will affect these responses to a different degree. Thus, regulation of PGE biosynthesis may also serve to alter the balance or in a sense discriminate among the responses to vasopressin.

Abnormalities of metabolism of arachidonic acid or its derivatives may affect water permeability profoundly. High concentrations of thromboxane A_2 or very high concentrations of PGE would have a vasopressin-like effect on water permeability; lower but elevated levels of PGE would inhibit the response to vasopressin; abnormally low levels of PGE would result in loss of the dampening effect.

Many issues remain unresolved. Among these are the effect of vasopressin on the metabolism of arachidonic acid and its derivatives in epithelial cells and the specific effect of other derivatives such as thromboxane A_2. Perhaps the most important advance will be the development of a better preparation for studying interactions between vasopressin, arachidonic acid and PG in renal epithelia.

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